

A Vankel dissolution tester (VanKel Industries, Edison, N.J.) was used for all dissolution studies. The apparatus was calibrated according to USP 23. The dissolution in 0.1N hydrochloric acid (pH 1.1) with 0.1% Tween 80 or pH 6.8 phosphate buffer with 0.1% Tween 80 was tested using the paddle method (USP Apparatus II), employing 900 ml of dissolution medium at a temperature of 37° C., and an agitation rate of 100 rpm. Samples at specific time points

were removed and filtered through a 70 μ m filter. The filtered samples were kept in screw cap glass test tubes until analysis. An HPLC system composed of an autosampler and a pump and a UV detector was used for sample analysis. 20 μ l of the dissolution samples were injected directly on the HPLC C18 column using a mixture of acetonitrile and ammonium acetate buffer (36:64) as the mobile phase.

The dissolution data are given in Table 4 below.

TABLE 4

Dissolution Data for Anagrelide Sustained Release Tablets								
	PD0073-55A		PD0073-57A		PD0073-64A		PD0073-78A	
Time (hour)	1*	2**	1	2	1	2	1	2
0.5	N/A	4.0 \pm 0.6	6.0 \pm 0.0	2.0 \pm 0.0	27.0 \pm 2.1	5.0 \pm 1.0	16.0 \pm 0.6	12.0 \pm 1.2
1.0	13.0 \pm 0.6	6.0 \pm 0.0	9.0 \pm 0.6	3.0 \pm 0.0	39.0 \pm 3.1	11.0 \pm 2.9	27.0 \pm 1.5	30.0 \pm 1.0
2.0	21.0 \pm 0.6	10.0 \pm 0.6	15.0 \pm 0.6	7.0 \pm 0.0	52.0 \pm 4.5	31.0 \pm 3.2	43.0 \pm 3.6	56.0 \pm 1.7
4.0	40.0 \pm 2.5	22.0 \pm 1.2	30.0 \pm 2.3	16.0 \pm 0.6	69.0 \pm 5.3	58.0 \pm 3.5	55.0 \pm 4.4	72.0 \pm 1.2
8.0	72.0 \pm 5.0	57.0 \pm 7.4	57.0 \pm 2.0	39.0 \pm 1.0	85.0 \pm 2.6	73.0 \pm 2.6	67 \pm 5.5	78.0 \pm 0.6
12.0	95.0 \pm 2.9	77.0 \pm 5.3	77.0 \pm 2.1	62.0 \pm 3.6	88.0 \pm 1.0	79.0 \pm 2.1	83 \pm 3.6	82.0 \pm 0.0

*1 = percent dissolved using a pH 1.1 dissolution medium with 0.1% Tween 80.

**2 = percent dissolved using a pH 6.8 dissolution medium with 0.1% Tween 80.

Note:

The data represent the mean percent dissolved \pm standard deviation of three replicates.

It is to be understood, however, that the scope of the present invention is not to be limited to the specific embodiments described above. The invention may be practiced other than as particularly described and still be within the scope of the accompanying claims.

What is claimed is:

1. A pharmaceutical composition, comprising:

(a) at least one pharmaceutically active agent that is pH dependent:

(b) at least one non-pH dependent sustained release agent; and

(c) at least one pH dependent agent that increases the rate of release of said at least one pharmaceutically active agent from the tablet at a pH in excess of 5.5.

2. The composition of claim 1 wherein said at least one pH dependent agent is at least one polymer that swells at a pH in excess of 5.5.

3. The composition of claim 1 wherein said at least one pH dependent agent is at least one enteric agent.

4. The composition of claim 1 wherein said at least one pH dependent agent is at least one agent that increases the solubility of said at least one pharmaceutically active agent at a pH of greater than 5.5.

5. The composition of claim 1 wherein said at least one pharmaceutically active agent is selected from the group consisting of guanfacine hydrochloride, anagrelide, guanethidine monosulfate, guanadrel sulfate, reserpine, propranolol, metoprolol, atenolol, timolol, erythromycin, clonidine, chlorpheniramine, bromopheniramine, diltiazem, and scopolamine.

6. The composition of claim 5 wherein said at least one pharmaceutically active agent guanfacine hydrochloride.

7. The composition of claim 5 wherein said at least one pharmaceutically active agent is anagrelide hydrochloride.

8. The composition of claim 1 wherein said non-pH dependent sustained release agent is selected from the group consisting of ethylcellulose, cellulose acetate, vinyl acetate/vinyl chloride copolymers, acrylate/methacrylate copolymers, polyethylene oxide, hydroxypropyl methylcellulose, carageenan, alginic acid and salts thereof,

hydroxyethyl cellulose, hydroxypropyl cellulose, karaya gum, acacia gum, tragacanth gum, locust bean gum, guar gum, sodium carboxymethyl cellulose, methyl cellulose, beeswax, carnauba wax, cetyl alcohol, hydrogenated vegetable oils, and stearyl alcohol.

9. The composition of claim 2 wherein said at least one polymer that swells at a pH in excess of 5.5 is selected from the group consisting of acrylic acid copolymers, sodium alginate, carrageenan, alginic acid, pectin, and sodium carboxymethyl cellulose.

10. The composition of claim 3 wherein said at least one enteric agent is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, methacrylic acid copolymers, cellulose acetate trimellitate, hydroxypropyl methylcellulose acetate, succinate, shellac, and zein.

11. The composition of claim 4 wherein said at least one agent that increase the solubility of said at least one pharmaceutically active agent at a pH greater than 5.5 is at least one organic acid.

12. The composition of claim 11 wherein said at least one organic acid is selected from the group consisting of citric acid, fumaric acid, tartaric acid, adipic acid, glucono delta-lactone, and malic acid.

13. The composition of claim wherein said pH-dependent agent that increase the rate of release of the at least one pharmaceutically active agent from the tablet at a pH in excess of 5.5 is an agent that maintains an acidic microenvironment in the composition.

14. The composition of claim 12 wherein said organic acid is fumaric acid.

15. The composition of claim 1 and further comprising a binding agent.

16. The composition of claim 15 wherein said binding agent is selected from the group consisting of polyvinyl pyrrolidone, starch, methylcellulose, hydroxypropyl methylcellulose, carboxymethyl cellulose, sucrose solution, dextrose solution, acacia, tragacanth, and locust bean gum.

17. The composition of claim 16 wherein said binder is hydroxypropyl methylcellulose.

18. The composition of claim 1 wherein said pharmaceutically active agent is present in the composition in an amount of from about 0.1 wt. % to about 70 wt. %.